

STIC Search Report Biotech-Chem Library

STIC Database Tracking Number: 143082

TO: Zohreh Fay

Location: 3a61 / 3c70

Tuesday, January 25, 2005

Art Unit: 1614 Phone: 272-0573

Serial Number: 10 / 039827

From: Jan Delaval

Location: Biotech-Chem Library

Rem 1a51

Phone: 272-2504

jan.delaval@uspto.gov

Search Notes									





STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact the searcher or contact:

Mary Hale, Information Branch Supervisor Remsen Bldg. 01 D86 571-272-2507

Voluntary Results Feedback Form

>	I am an examiner in Workgroup: Example: 1610
>	Relevant prior art found, search results used as follows:
	☐ 102 rejection
	103 rejection
	Cited as being of interest.
	Helped examiner better understand the invention.
	Helped examiner better understand the state of the art in their technology.
	Types of relevant prior art found:
	☐ Foreign Patent(s)
٠	 Non-Patent Literature (journal articles, conference proceedings, new product announcements etc.)
>	Relevant prior art not found:
	Results verified the lack of relevant prior art (helped determine patentability).
	Results were not useful in determining patentability or understanding the invention.
C	omments:

Drop off or send completed forms to STIC-Blotech-Chem Library Remsen Bidg.



143082

SEARCH REQUEST FORM

Scientific and Technical Information Center

		car thiormation Center	
Requester's Full Name: Art Unit: 16/01 Ph Mini Box and Bldg Room Loc If more than one search is s	one Number 345 71-7 cation: 3C70	Examiner # : 6664 72-0513 Serial Number: 10 Results Format Preferred tene oritize searches in order of	6 Date 1/25/05 2/63 9 1/827 Dec PAPER DISK L-MAH
Please provide a detailed statement of Include the elected species or structurations of the invention. Define any freeze Please attach a copy of the c	of the search topic, and des tres, keywords, synonyms, terms that may have a spec- over sheet, pertinent chains	scribe as specifically as possible the sacronyms, and registry numbers, and internating. Give examples or relevant	adject matter to be search of d combine with the concept of said estations, authors on a search of said estations.
Title of Invention: Nette Inventors (please provide full page)	ds and composition	tions for medulation	Jepha Josephin :
Wen Ku, Keni Cal	10/19/2001	; wheeler, Larry	——————————————————————————————————————
For Sequence Searches Only Pleases appropriate serial number.	ifelude all pertinent informa	tion (parent, child, divisional, or issued	Datent number 1 of
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1-3 and the met		- 1 claims 4-6	
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STAFF USE ONLY Searcher Searcher Phone # 22804 Searcher Location Oate Searcher Picked Up //25/65 sete Completed: //75/45 Searcher Prep & Review Time Tencal Prep Time // O Online 1(1) // O PIGE (SPE) (X (I))	Type of Search NA Sequence (#) AA Sequence (#) Structure (#) Bibliographic Litigation Fulltext Patent Family Other	Vendors and cost wher STN Dialog Questel/Orbit Dr.L.ink Lexis/Nexis Sequence Systems WWW/Internet Other (specify)	

=> fil reg FILE 'REGISTRY' ENTERED AT 09:12:25 ON 25 JAN 2005 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 JAN 2005 HIGHEST RN 819046-01-0 DICTIONARY FILE UPDATES: 23 JAN 2005 HIGHEST RN 819046-01-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at: http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot 112

L12 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN

RN 366786-91-6 REGISTRY

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

FS 3D CONCORD

MF C10 H12 Cl F N2 O S

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPAT7ULL

DT.CA CAplus document type: Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

- 7 REFERENCES IN FILE CA (1907 TO DATE)
- 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
- 7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:332518

REFERENCE 2: 140:13072

REFERENCE 3: 138:331737

REFERENCE 4: 137:73273

REFERENCE 5: 136:363872

REFERENCE 6: 135:327361

REFERENCE 7: 135:298811

L12 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN

RN 61290-32-2 REGISTRY

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

FS 3D CONCORD

MF C10 H13 F N2 O S

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)

DT.CA CAplus document type: Conference; Journal; Patent

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

- 8 REFERENCES IN FILE CA (1907 TO DATE)
- 2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
- 8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:331737

REFERENCE 2: 137:73273

REFERENCE 3: 136:363872

REFERENCE 4: 135:327361

REFERENCE 5: 135:298811

REFERENCE 6: 93:142669

REFERENCE 7: 93:132428

REFERENCE 8: 86:16440

=> d his

(FILE 'HOME' ENTERED AT 09:06:08 ON 25 JAN 2005) SET COST OFF

FILE 'HCAPLUS' ENTERED AT 09:06:36 ON 25 JAN 2005

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L1
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L2
            228 $ E3-E19
                E CHOW KEN/AU
             47 S E3-E14
L3
                E GIL D/AU
L4
             65 S E3, E6, E9, E11-E13
                E FANG W/AU
             66 S E3
L5
                E FANG WEN/AU
             17 S E3, E13
L6
                E FANG WENKUI/AU
              7 S E3, E4
L7
                E GARST M/AU
            128 S E3, E4, E7-E9
L8
                E WHEELER L/AU
            105 S E3, E4, E13-E15, E20
L9
                E ALLERG/PA, CS
                E ALLERGA/PA,CS
            941 S ALLERGAN?/PA,CS
L10
                SEL RN L1
     FILE 'REGISTRY' ENTERED AT 09:09:12 ON 25 JAN 2005
              5 S E1-E5
L11
              2 S L11 AND (C10H12CLFN2OS OR C10H13FN2OS)
L12
L13
              0 S (61290-32-2 OR 366786-91-6)/CRN
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L14
              0 S L12
     FILE 'HCAPLUS' ENTERED AT 09:10:44 ON 25 JAN 2005
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L15
              7 S L1-L10 AND L15
L16
L17
              8 S L15, L16 AND (PD<=20011019 OR PRD<=20011019 OR AD<=20011019)
              2 S L15, L16 NOT L17
L18
L19
             10 S L17, L18
     FILE 'USPATFULL' ENTERED AT 09:11:50 ON 25 JAN 2005
L20
              8 S L12
     FILE 'REGISTRY' ENTERED AT 09:12:25 ON 25 JAN 2005
=> fil uspatfull
FILE 'USPATFULL' ENTERED AT 09:12:37 ON 25 JAN 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 20 Jan 2005 (20050120/PD)
FILE LAST UPDATED: 20 Jan 2005 (20050120/ED)
HIGHEST GRANTED PATENT NUMBER: US6845512
HIGHEST APPLICATION PUBLICATION NUMBER: US2005015836
CA INDEXING IS CURRENT THROUGH 20 Jan 2005 (20050120/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 20 Jan 2005 (20050120/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2004
>>> USPAT2 is now available. USPATFULL contains full text of the
                                                                        <<<
>>> original, i.e., the earliest published granted patents or
                                                                        <<<
>>> applications. USPAT2 contains full text of the latest US
                                                                        <<<
>>> publications, starting in 2001, for the inventions covered in
                                                                        <<<
>>> USPATFULL. A USPATFULL record contains not only the original
                                                                        <<<
>>> published document but also a list of any subsequent
                                                                        <<<
>>> publications. The publication number, patent kind code, and
                                                                        <<<
>>> publication date for all the US publications for an invention
                                                                        <<<
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>>> are displayed in the PI (Patent Information) field of USPATFULL >>> records and may be searched in standard search fields, e.g., /PN, /PK, etc. <<< >>> USPATFULL and USPAT2 can be accessed and searched together >>> <<< through the new cluster USPATALL. Type FILE USPATALL to <<< enter this cluster. <<< >>> >>> <<< Use USPATALL when searching terms such as patent assignees, >>> <<< classifications, or claims, that may potentially change from >>> <<< the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d 120 bib abs hitstr tot

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L20
     ANSWER 1 OF 8 USPATFULL on STN
       2004:223761 USPATFULL
AN
ΤI
       Agent and methods for treating pain
       Gil, Daniel W., Corona Del Mar, CA, United States
IN
       Aoki, Kei R., Coto de Caza, CA, United States
       Allergan, Inc., Irvine, CA, United States (U.S. corporation)
PA
PΙ
       US 6787517
                          В1
                                20040907
       US 2000-751053
                               20001229 (9)
ΑI
       Utility
DT
FS
       GRANTED
EXNAM Primary Examiner: Riley, Jezia
LREP
       Stout, Uxa, Buyan & Mullins, LLP, Uxa, Frank J., Hollrigel, Greq S.
CLMN
       Number of Claims: 46
ECL
       Exemplary Claim: 1
DRWN
       1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1772
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AΒ
       Agents for treating pain, methods for producing the agents and methods
```

Agents for treating pain, methods for producing the agents and methods for treating pain by administration to a patient of a therapeutically effective amount of the agent are disclosed. The agent may include a clostridial neurotoxin, a fragment or a derivative thereof, attached to a targeting component, wherein the targeting component is selected from a group consisting of compounds which selectively binds at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to other binding sites, for example, the alpha-2A adrenergic receptor subtype.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 61290-32-2D, conjugates 366786-91-6D, conjugates

(adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

RN 61290-32-2 USPATFULL

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-91-6 USPATFULL CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

L20 ANSWER 2 OF 8 USPATFULL on STN

AN 2004:189764 USPATFULL

TI Agents and methods for treating pain

IN Gil, Daniel W., Corona Del Mar, CA, UNITED STATES Aoki, Kei R., Coto de Caza, CA, UNITED STATES

PA Allergan Sales, Inc., Irvine, CA, 92612 (U.S. corporation)

PI US 2004146532 A1 20040729

AI US 2004-791434 A1 20040301 (10)

RLI Division of Ser. No. US 2000-751053, filed on 29 Dec 2000, PENDING

DT Utility

FS APPLICATION

LREP Frank J. Uxa, Stout, Uxa, Buyan & Mullins, LLP, Suite 300, 4 Venture, Irvine, CA, 92618

CLMN Number of Claims: 67 ECL Exemplary Claim: 1 DRWN 1 Drawing Page(s)

LN.CNT 1856

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Agents for treating pain, methods for producing the agents and methods for treating pain by administration to a patient of a therapeutically effective amount of the agent are disclosed. The agent may include a clostridial neurotoxin, a fragment or a derivative thereof, attached to a targeting component, wherein the targeting component is selected from a group consisting of compounds which selectively binds at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to other binding sites, for example, the alpha-2A adrenergic receptor subtype.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 61290-32-2D, conjugates 366786-91-6D, conjugates

(adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

RN 61290-32-2 USPATFULL

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

L20 ANSWER 3 OF 8 USPATFULL on STN ΑN 2004:179142 USPATFULL ΤI Methods for the treatment of neurodegeneration Wheeler, Larry A., Irvine, CA, UNITED STATES TN Gil, Daniel W., Corona Del Mar, CA, UNITED STATES Donello, John E., Dana Point, CA, UNITED STATES US 2004138312 20040715 PΤ A1 ΑI US 2003-680879 A1 20031007 (10) US 2002-417049P 20021008 (60) PRAI Utility DTAPPLICATION FS Carlos A. Fisher, ALLERGAN, INC., T2-7H, 2525 Dupont Drive, Irvine, CA, LREP Number of Claims: 15 CLMN Exemplary Claim: 1 ECL No Drawings DRWN LN.CNT 681 CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB Methods of preventing or retarding the degeneration of neurons. Also disclosed are methods for treating Alzheimer's disease or Parkinson's disease through the administration of selective alpha 2B or alpha 2B/2C receptor agonists, hereby incorporated by reference herein. CAS INDEXING IS AVAILABLE FOR THIS PATENT. IT 366786-91-6

 $(\alpha 2B \text{ or } \alpha 2B/2C \text{ adrenoceptor agonists for treatment of}$ neurodegeneration)

RN366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
 \downarrow $CH_2-NH-C-NH-CH_2-CH_2-OH$

L20 ANSWER 4 OF 8 USPATFULL on STN AN 2004:172660 USPATFULL ΤI Novel methods and compositions for alleviating pain Gil, Daniel W., Corona Del Mar, CA, UNITED STATES IN Donello, John E., Dana Point, CA, UNITED STATES Allergan, Inc. (U.S. corporation) PA 20040708 PΙ US 2004132824 A1 20031211 (10) AΙ US 2003-735506 **A1** Division of Ser. No. US 2002-153154, filed on 21 May 2002, PENDING RLI DTUtility FS APPLICATION Cathryn Campbell, McDERMOTT, WILL & EMERY, 4370 La Jolla Village Drive, LREP

7th Floor, San Diego, CA, 92122

CLMN Number of Claims: 114 ECL Exemplary Claim: 1 DRWN 15 Drawing Page(s)

LN.CNT 2796

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

The present invention provides a method for the long-term relief of chronic pain in a subject by activating in the subject an analgesic α -adrenergic receptor in the absence of α -2A receptor activation over a period of at least three days, such that relief of chronic pain is maintained in the absence of continued activation of said receptor. The analgesic α -adrenergic receptor can be, for example, the α -2B receptor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 366786-91-6

 $(\alpha$ -adrenoceptor activation for alleviating pain)

RN 366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
 \downarrow $CH_2-NH-C-NH-CH_2-CH_2-OH$

L20 ANSWER 5 OF 8 USPATFULL on STN

AN 2003:325106 USPATFULL

TI Novel methods and compositions for alleviating pain

IN Gil, Daniel W., Corona Del Mar, CA, UNITED STATES

Donello, John E., Dana Point, CA, UNITED STATES

PI US 2003229088 A1 20031211

AI US 2002-153154 A1 20020521 (10)

DT Utility

FS APPLICATION

LREP CAMPBELL & FLORES LLP, 4370 LA JOLLA VILLAGE DRIVE, 7TH FLOOR, SAN DIEGO, CA, 92122

CLMN Number of Claims: 114

ECL Exemplary Claim: 1

DRWN 15 Drawing Page(s)

LN.CNT 2794

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

The present invention provides a method for the long-term relief of chronic pain in a subject by activating in the subject an analgesic α -adrenergic receptor in the absence of α -2A receptor activation over a period of at least three days, such that relief of chronic pain is maintained in the absence of continued activation of said receptor. The analgesic α -adrenergic receptor can be, for example, the α -2B receptor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 366786-91-6

 $(\alpha$ -adrenoceptor activation for alleviating pain)

RN 366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
 \downarrow $CH_2-NH-C-NH-CH_2-CH_2-OH$

L20 ANSWER 6 OF 8 USPATFULL on STN

AN 2003:134677 USPATFULL

TI Methods and compositions for modulating alpha adrenergic receptor

activity

IN Chow, Ken, Newport Coast, CA, UNITED STATES

Gil, Daniel W., Corona Del Mar, CA, UNITED STATES

Fang, Wenkui Ken, Irvine, CA, UNITED STATES

Garst, Michael E., Newport Beach, CA, UNITED STATES

Wheeler, Larry A., Irvine, CA, UNITED STATES

PI US 2003092766 A1 20030515

AI US 2001-39827 A1 20011019 (10)

DT Utility

FS APPLICATION

LREP Carlos A. Fisher, ALLERGAN, INC., T2-7H, 2525 Dupont Drive, Irvine, CA,

92612

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 670

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the treatment of pain and intraocular pressure. Particularly disclosed are new compositions for the treatment of chronic pain, glaucoma and methods for their use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 61290-32-2P 366786-91-6P

(thiourea derivs., preparation and use in treatment of glaucoma and pain)

RN 61290-32-2 USPATFULL

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

(thiourea derivs., prepn. and use in treatment of glaucoma and pain)

L20 ANSWER 7 OF 8 USPATFULL on STN
AN 2002:113091 USPATFULL
TI Methods and compositions for a

Methods and compositions for modulating alpha adrenergic receptor activity

IN Chow, Ken, Newport Coast, CA, UNITED STATES
Gil, Daniel W., Corona Del Mar, CA, UNITED STATES
Fang, Wenkui, Irvine, CA, UNITED STATES

Garst, Michael E., Newport Beach, CA, UNITED STATES

Wheeler, Larry A., Irvine, CA, UNITED STATES

PA ALLERGAN SALES, INC. (U.S. corporation)

PI US 2002058839 A1 20020516 US 6545182 B2 20030408

AI US 2001-778975 A1 20010205 (9)

RLI Continuation-in-part of Ser. No. US 2000-548315, filed on 13 Apr 2000, ABANDONED

DT Utility

FS APPLICATION

LREP Carlos A. Fisher, ALLERGAN, INC., T2-2E, 2525 Dupont Drive, Irvine, CA, 92623

CLMN Number of Claims: 18 ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 782

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the treatment of pain. Particularly disclosed are new compositions for the treatment of chronic pain, and methods for their use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 61290-32-2P 366786-91-6P

(preparation of thiourea compds. for modulating α -adrenergic receptor activity and use in treatment of pain)

RN 61290-32-2 USPATFULL

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

L20 ANSWER 8 OF 8 USPATFULL on STN

AN 2001:197069 USPATFULL

TI Methods and compositions for modulating alpha adrenergic receptor

activity

IN Chow, Ken, Newport Coast, CA, United States

Gil, Daniel W., Corona Del Mar, CA, United States

Fang, Wenkui Ken, Irvine, CA, United States

Garst, Michael E., Newport Beach, CA, United States

Wheeler, Larry A., Irvine, CA, United States

PA Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)

PI US 6313172 B1 20011106

AI US 2000-548410 20000413 (9)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Vollano, Jean F.

LREP Fisher, Carlos A., Baran, Robert J., Voet, Martin A.

CLMN Number of Claims: 10 ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 542

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the treatment of pain using this area derivatives. Particularly disclosed are new compositions for the treatment of chronic pain, and methods for their use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 61290-32-2P 366786-91-6P

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

RN 61290-32-2 USPATFULL

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 USPATFULL

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
 $CH_2-NH-C-NH-CH_2-CH_2-OH$

IT 61290-32-2D, alkyl esters 366786-91-6D, alkyl esters

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

RN 61290-32-2 USPATFULL

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2 - NH - C - NH - CH_2 - CH_2 - OH$$

RN 366786-91-6 USPATFULL CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

C1
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

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FILE COVERS 1907 - 25 Jan 2005 VOL 142 ISS 5 FILE LAST UPDATED: 24 Jan 2005 (20050124/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L19 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:331968 HCAPLUS

DN 140:332518

ED Entered STN: 23 Apr 2004

TI α 2B or α 2B/2C Adrenoceptor agonists for the treatment of neurodegeneration

IN Wheeler, Larry A.; Gil, Daniel W.; Donello, John E.

PA Allergan, Inc., USA

SO PCT Int. Appl., 36 pp. CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-17

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ICS A61K031-4174; A61P025-16; A61P025-28
     1-11 (Pharmacology)
CC
FAN.CNT 1
     PATENT NO.
                        KIND
                                 DATE
                                          APPLICATION NO.
                                                                    DATE
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      . . . . . . . . . . . . . . . . . . .
                                 ----
                                             ______
                                                                     _____
                                 20040422 WO 2003-US31809
     WO 2004032913
                          A1
                                                                    20031007
PΙ
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             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
                          A1
                                 20040715
                                             US 2003-680879
                                                                      20031007
     US 2004138312
PRAI US 2002-417049P
                           Р
                                 20021008
CLASS
               CLASS PATENT FAMILY CLASSIFICATION CODES
 PATENT NO.
 -----
 WO 2004032913 ICM
                         A61K031-17
                 ICS
                         A61K031-4174; A61P025-16; A61P025-28
     The invention discloses methods using \alpha 2B or \alpha 2B/2C
AB
     adrenoceptor agonists for preventing or retarding the degeneration of
     neurons. Also disclosed are methods for treating Alzheimer's disease or
     Parkinson's disease through the administration of selective \alpha 2B or
     \alpha2B/2C adrenoceptor agonists.
ST
     neurodegeneration neuroprotectant adrenergic 2B 2C agonist; Alzheimer
     Parkinson drug adrenergic 2B 2C agonist
IT
     Nerve, disease
        (death; \alpha2B or \alpha2B/2C adrenoceptor agonists for treatment
        of neurodegeneration)
IT
     Brain, disease
     Nervous system, disease
        (degeneration; \alpha 2B or \alpha 2B/2C adrenoceptor agonists for
        treatment of neurodegeneration)
IT
     Brain
        (locus ceruleus; \alpha2B or \alpha2B/2C adrenoceptor agonists for
        treatment of neurodegeneration)
IT
     Cell death
        (neuron; \alpha2B or \alpha2B/2C adrenoceptor agonists for treatment
        of neurodegeneration)
     Cytoprotective agents
IT
        (neuroprotective; \alpha 2B or \alpha 2B/2C adrenoceptor agonists for
        treatment of neurodegeneration)
IT
     Mental activity
        (sedation; \alpha 2B or \alpha 2B/2C adrenoceptor agonists for
        treatment of neurodegeneration)
IT
     Brain
        (substantia nigra; \alpha2B or \alpha2B/2C adrenoceptor agonists for
        treatment of neurodegeneration)
IT
     Drug delivery systems
        (systemic; \alpha 2B or \alpha 2B/2C adrenoceptor agonists for
        treatment of neurodegeneration)
IT
     Ketones, biological studies
     Thiocarbonyl compounds
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (thiones; \alpha 2B or \alpha 2B/2C adrenoceptor agonists for treatment
        of neurodegeneration)
IT
     Brain
         (ventral tegmental area; \alpha 2B or \alpha 2B/2C adrenoceptor
```

agonists for treatment of neurodegeneration) Adrenoceptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (α 1; α 2B or α 2B/2C adrenoceptor agonists for treatment of neurodegeneration)

IT Adrenoceptor agonists

 $(\alpha 2-; \alpha 2B \text{ or } \alpha 2B/2C \text{ adrenoceptor agonists for treatment of neurodegeneration})$

IT Alzheimer's disease

Anti-Alzheimer's agents Antiparkinsonian agents Nervous system agents

Parkinson's disease

 $(\alpha 2B \text{ or } \alpha 2B/2C \text{ adrenoceptor agonists for treatment of neurodegeneration})$

IT Adrenoceptors

IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (α 2B; α 2B or α 2B/2C adrenoceptor agonists for treatment of neurodegeneration)

IT Adrenoceptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (α 2C; α 2B or α 2B/2C adrenoceptor agonists for treatment of neurodegeneration)

IT 113775-47-6, Dexmedetomidine

RL: BSU (Biological study, unclassified); BIOL (Biological study) (α 2B or α 2B/2C adrenoceptor agonists for treatment of neurodegeneration)

neurodegeneration)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

(1) Allergan Inc; WO 02076950 A 2002 HCAPLUS

(2) Allergan Inc; WO 03099795 A 2003 HCAPLUS

(3) Allergan Sales Inc; WO 9928300 A 1999 HCAPLUS

IT 366786-91-6

RE

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(g2B or g2B/2C adrenoceptor agonists for treatment of

 $(\alpha 2B \text{ or } \alpha 2B/2C \text{ adrenoceptor agonists for treatment of neurodegeneration})$

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

L19 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:950846 HCAPLUS

DN 140:13072

ED Entered STN: 07 Dec 2003

TI Novel methods and compositions for alleviating pain

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Gil, Daniel W.; Donello, John E.
ΤN
PA
    Allergan, Inc., USA
SO
     PCT Int. Appl., 129 pp.
     CODEN: PIXXD2
DT
     Patent
LA
     English
IC
     ICM A61K031-538
     ICS A61K031-4164; A61K031-4168; A61K031-4178; A61K031-498; A61K031-137;
         A61P029-00
CC
     1-11 (Pharmacology)
     Section cross-reference(s): 25
FAN.CNT 1
                                         APPLICATION NO.
     PATENT NO.
                       KIND DATE
                                                               DATE
                                          _____
                                                                 _____
                       ----
    WO 2003099289 A2 20031204 WO 2003-US13057
                                                               20030423
PΙ
                       A3
     WO 2003099289
                               20040318
        W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
            PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
            UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
            KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
            FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
            BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
                        A1 20031211 US 2002-153154 20020521
     US 2003229088
     US 2004132824
                         A1
                               20040708
                                         US 2003-735506
                                                                20031211
PRAI US 2002-153154
                         Α
                               20020521
CLASS
               CLASS PATENT FAMILY CLASSIFICATION CODES
 PATENT NO.
 ______
 WO 2003099289 ICM
                       A61K031-538
                       A61K031-4164; A61K031-4168; A61K031-4178; A61K031-498;
                ICS
                       A61K031-137; A61P029-00
     The invention provides a method for the long-term relief of chronic pain
AΒ
     in a subject by activating in the subject an analgesic \alpha-adrenergic
     receptor in the absence of \alpha-2A receptor activation over a period of
     at least three days, such that relief of chronic pain is maintained in the
     absence of continued activation of said receptor. The analgesic
     \alpha-adrenergic receptor can be, for example, the \alpha-2B receptor.
ST
     pain alleviation analgesic alpha adrenoceptor agonist antagonist
IT
     Pain
     Skin, disease
        (allodynia; α-adrenoceptor activation for alleviating pain)
IT
     Nerve, disease
        (diabetic neuropathy; α-adrenoceptor activation for alleviating
       pain)
IT
     Viscera
        (disease, pain; \alpha-adrenoceptor activation for alleviating pain)
IT
     Behavior
        (exploratory; α-adrenoceptor activation for alleviating pain)
IT
     Mutation
        (homozygous point mutation at \alpha-2A receptor locus, Asp79 to Asn
       mutation; \alpha-adrenoceptor activation for alleviating pain)
IT
     Drug delivery systems
        (injections, s.c., minipumps; \alpha-adrenoceptor activation for
        alleviating pain)
IT
     Nerve, disease
        (injury; \alpha-adrenoceptor activation for alleviating pain)
     Intestine, disease
IT
        (irritable bowel syndrome; \alpha-adrenoceptor activation for
        alleviating pain)
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IT
     Behavior
        (motor; \alpha-adrenoceptor activation for alleviating pain)
IT
     Nerve, disease
     Pain
        (neuralgia; \alpha-adrenoceptor activation for alleviating pain)
     Drug delivery systems
IT
        (oral; \alpha-adrenoceptor activation for alleviating pain)
     Arthritis
IT
     Inflammation
     Neoplasm
        (pain; \alpha-adrenoceptor activation for alleviating pain)
IT
     Pain
        (postoperative; α-adrenoceptor activation for alleviating pain)
IT
     Nerve
        (sciatic; \alpha-adrenoceptor activation for alleviating pain)
IT
     Pain
        (visceral; \alpha-adrenoceptor activation for alleviating pain)
TТ
     Animal
     Mus
        (wild; \alpha-adrenoceptor activation for alleviating pain)
IT
     Adrenoceptor agonists
        (\alpha-; \alpha-adrenoceptor activation for alleviating pain)
IT
     Analgesia
     Analgesics
     Headache
     Hypnotics and Sedatives
     Hypotension
        (\alpha-adrenoceptor activation for alleviating pain)
TТ
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\alpha1A; \alpha-adrenoceptor activation for alleviating pain)
TΤ
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\alpha1B; \alpha-adrenoceptor activation for alleviating pain)
IT
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\alpha1D; \alpha-adrenoceptor activation for alleviating pain)
IT
     Adrenoceptor antagonists
        (\alpha2-, \alpha-2A; \alpha-adrenoceptor activation for alleviating
        pain)
TT
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (\alpha2A; \alpha-adrenoceptor activation for alleviating pain)
TΤ
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\alpha2B, agonists; \alpha-adrenoceptor activation for alleviating
        pain)
TΤ
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\alpha2C, agonists; \alpha-adrenoceptor activation for alleviating
        pain)
     62-56-6, Thiourea, biological studies 62-56-6D, Thiourea, derivs.
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (\alpha-adrenoceptor activation for alleviating pain)
TΤ
     51-41-2, Norepinephrine 4205-90-7, Clonidine 51322-75-9, Tizanidine
                               113775-47-6, Dexmedetomidine
                                                                 159091-94-8
     59803-98-4, Brimonidine
                                  226571-24-0D, stereoisomers
     168570-37-4
                   226571-24-0
                                 423773-40-4D, stereoisomers
     366786-91-6
                  423773-40-4
     423773-41-5 423773-41-5D, stereoisomers 628730-19-8
                                                                   628730-19-8D,
     stereoisomers 628730-30-3 628730-35-8
                                                    628730-36-9
                                                                   629628-13-3
                                     629628-14-4
                                                    629628-15-5
                                                                   629628-16-6
     629628-13-3D, stereoisomers
     629628-17-7 629628-18-8 630410-33-2, BRL 48962
                                                           630410-33-2D, BRL
     48962, esters, amides and stereoisomers
```

$$\texttt{C1} \qquad \qquad \overset{\texttt{F}}{\overset{\texttt{S}}{\parallel}} \qquad \qquad \overset{\texttt{S}}{\overset{\texttt{S}}{\parallel}} \qquad \qquad \\ \texttt{CH}_2 - \texttt{NH} - \texttt{C} - \texttt{NH} - \texttt{CH}_2 - \texttt{CH}_2 - \texttt{OH}$$

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ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
L19
    2003:334962 HCAPLUS
AN
DN
    138:331737
    Entered STN: 02 May 2003
ED
    Methods and compositions for modulating \alpha adrenergic receptor
ΤT
    activity, and therapeutic use thereof
    Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken;
TN
    Garst, Michael E.; Wheeler, Larry A.
PΑ
    Allergan, Inc., USA
    PCT Int. Appl., 35 pp.
SO
    CODEN: PIXXD2
DT
    Patent
    English
LA
IC
    ICM A61P027-06
     ICS A61K031-17; A61K031-222
     1-12 (Pharmacology)
CC
    Section cross-reference(s): 63
FAN.CNT 1
    PATENT NO.
                       KIND DATE
                                        APPLICATION NO.
                                                              DATE
     ______
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                                         -----
                                                               -----
                                        WO 2002-US32571
PΙ
    WO 2003035178
                        A1
                              20030501
                                                               20021011 <--
        W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
            PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
            UA, UG, UZ, VN, YU, ZA, ZM, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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            FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
            CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
                              20030515
    US 2003092766
                        A1
                                       US 2001-39827
                                                               20011019 <--
PRAI US 2001-39827
                              20011019 <--
                        Α
CLASS
PATENT NO.
               CLASS PATENT FAMILY CLASSIFICATION CODES
               ____
                      ______
WO 2003035178
                ICM
                      A61P027-06
                      A61K031-17; A61K031-222
                ICS
               ECLA
US 2003092766
                      A61K031/17
                                                                        <--
os
    MARPAT 138:331737
GΙ
```

AB Methods and compns. are discloses for the treatment of pain and intraocular pressure. Particularly disclosed are compns. for the treatment of chronic pain, glaucoma, and methods for their use. Compds of the invention include e.g. I (preparation given).

ST thiourea deriv prepn chronic pain glaucoma; alpha adrenergic ligand therapeutic pain intraocular pressure

IT Pain

IT

IT

RN

(chronic; thiourea derivs., preparation and use in treatment of glaucoma and pain)

IT Analgesics

Antiglaucoma agents Drug delivery systems Glaucoma (disease) Pain

(thiourea derivs., preparation and use in treatment of glaucoma and pain) 61290-32-2P 366786-91-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(thiourea derivs., preparation and use in treatment of glaucoma and pain) 366786-91-6D, alkyl esters

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thiourea derivs., preparation and use in treatment of glaucoma and pain)

IT 141-43-5, Ethanolamine, reactions 2740-88-7, 4-Fluorobenzyl isothiocyanate 366787-56-6

RL: RCT (Reactant); RACT (Reactant or reagent)

Ι

(thiourea derivs., preparation and use in treatment of glaucoma and pain) RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD RE

- (1) Allergan Sales Inc; WO 0178702 A 2001 HCAPLUS
- (2) Allergan Sales Inc; WO 0178703 A 2001 HCAPLUS
- (3) Egyt Gyogyszervegyeszeti Gyar; GB 1499485 A 1978 HCAPLUS
- (4) Reiter, J; EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY 1980, V15(1), P41 HCAPLUS
- IT 61290-32-2P 366786-91-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(thiourea derivs., preparation and use in treatment of glaucoma and pain) 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

366786-91-6 HCAPLUS RN

Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) CN (CA INDEX NAME)

$$\texttt{C1} \qquad \qquad \overset{\texttt{F}}{\underset{\texttt{CH}_2-\texttt{NH}-\texttt{C}-\texttt{NH}-\texttt{CH}_2-\texttt{CH}_2-\texttt{OH}}{\texttt{CH}_2-\texttt{NH}-\texttt{CH}_2-\texttt{CH}_2-\texttt{OH}}}$$

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thiourea derivs., prepn. and use in treatment of glaucoma and pain

ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN L19

2002:521523 HCAPLUS AN

DN 137:73273

Entered STN: 12 Jul 2002 ED

Adrenergic receptor ligand-neurotoxin conjugates and methods for treating ΤI pain

Gil, Daniel W.; Aoki, Kei Roger IN

Allergan Sales, Inc., USA PA

PCT Int. Appl., 76 pp. so

CODEN: PIXXD2

DTPatent

English LA

IC ICM A61K039-00

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

FAN.	AN.CNT 1																	
	PA	TENT	NO.						APPLICATION NO.						DATE			
ΡI	WO	2002053177			7 A2 20020711			WO 2001-US48651						20011214 <				
	WO	2002	0531	77		A3 20030918												
		W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	ΒZ,	CA,	CH,	CN,
			CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	ES,	FI,	GB,	GD,	GE,	GH,
			GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	ΚP,	KR,	ΚZ,	LC,	LK,	LR,
			LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PL,	PT,
			RO,	RŲ,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,	UZ,
			VN,	YU,	ZA,	ZW												
		RW:	GH,	GM,	KΕ,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	BY,
			KG,	ΚZ,	MD,	RU,	TJ,	TM,	ΑT,	BE,	CH,	CY,	DE,	DK,	ES,	FI,	FR,	GB,
			GR,	ΙE,	IT,	LU,	MC,	NL;	PT,	SE,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,
			GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG							
		6787								US 2000-751053								
									CA 2001-2433332									
	EP	1363	674			A2		2003	1126		EP 2001-990212				20011214 <			
		R:	•	•	•	•	•	•		•		-	LI,	LU,	NL,	SE,	MC,	PT,
			•	•	•	LV, FI, RO, MK,			CY, AL, TR									
				-		A1 20040729			US 2004-791434					20040301 <				
PRAI	US	2000-751053 A 20001229) <													

WO 2001-US48651 W 20011214 CLASS PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES WO 2002053177 ICM A61K039-00 A61K035/74; A61K038/16C; A61K047/48H4; A61K047/48R2D; US 6787517 ECLA A61K047/48T2C12P4; A61K047/48T4B18; C07K016/18 US 2004146532 ECLA A61K035/74; A61K038/16C; A61K047/48H4; A61K047/48R2D; A61K047/48T2C12P4; A61K047/48T4B18; C07K016/18 os MARPAT 137:73273 AB Agents for treating pain, methods for producing the agents, and methods for treating pain by administration to a patient of a therapeutically effective amount of the agent, are disclosed. The agent may include a clostridial neurotoxin, a fragment or a derivative thereof, attached to a targeting component, wherein the targeting component is selected form a group consisting of compds. which selectively binds at the $\alpha 2b$ or $\alpha 2b/\alpha 2c$ adrenergic receptor subtype(s) as compared to other binding sites, e.g. the $\alpha 2a$ adrenergic receptor subtype. ST adrenergic receptor ligand neurotoxin conjugate analgesic IT Proteins RL: BSU (Biological study, unclassified); BIOL (Biological study) (MBP (maltose-binding protein), fusion products; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) Analgesics IT Cytoplasm Drug delivery systems Human Ribosome (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) Amino acids, biological studies IT Gene Neurotransmitters RL: BSU (Biological study, unclassified); BIOL (Biological study) (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) Antibodies and Immunoglobulins IT RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Pain Skin, disease (allodynia; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) TT Toxins RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (butyricum, conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Pain (chronic; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) TΤ Hemocyanins RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses) (conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) TT Peptides, biological studies RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Proteins

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT (disease, pain; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Drug delivery systems (injections, i.m.; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Drug delivery systems (injections, s.c.; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Biological transport (intracellular; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) Drug delivery systems IT (intrathecal; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Nerve, disease (neuropathy, neuropathic pain; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT (referred; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) Proteins IT RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (saporins, conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Hydrocarbons, biological studies RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (spacer; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Toxins RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (tetanus, conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Pain (visceral; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Antigens RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses) (α2b receptor second extracellular loop; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Adrenoceptors RL: BSU (Biological study, unclassified); BIOL (Biological study) (α2B; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT Adrenoceptors RL: BSU (Biological study, unclassified); BIOL (Biological study) (α2C; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) IT 440645-44-3 RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses) (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain) 19216-56-9D, Prazosin, conjugates 61290-32-2D, conjugates TT

67339-62-2D, ARC 239, conjugates 81167-16-0D, Imiloxan, conjugates

93384-44-2D, Botulin B, conjugates

93384-47-5D, Botulin E, conjugates

93384-43-1D, Botulin A, conjugates

93384-46-4D, Botulin D, conjugates

107231-12-9D, Botulin, conjugates 107231-13-0D, Botulin C1, conjugates 107231-15-2D, Botulin F, conjugates 107231-16-3D, Botulin G, conjugates 366786-91-6D, conjugates RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)
147-85-3, L-Proline, biological studies RL: BSU (Biological study, unclassified); BIOL (Biological study) (proline-containing polypeptide, spacer; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)
61290-32-2D, conjugates 366786-91-6D, conjugates RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (adrenergic receptor ligand-neurotoxin conjugates and methods for

treating pain)
RN 61290-32-2 HCAPLUS

TT

IT

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 HCAPLUS
CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN L19 AN2002:369027 HCAPLUS DN 136:363872 EDEntered STN: 18 May 2002 TI Preparation of thiourea compounds for modulating α -adrenergic receptor activity and use in the treatment of pain Chow, Ken; Gil, Daniel W.; Fang, Wenkui; IN Garst, Michael E.; Wheeler, Larry A. PAAllergan Sales, Inc., USA SO U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 548,315, abandoned. CODEN: USXXCO DTPatent LΑ English IC ICM A61K031-17 ICS C07C275-24 NCL 564047000 CC 1-11 (Pharmacology) Section cross-reference(s): 25, 63 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	PI US 2002058839 US 6545182			20020516	US 2001-778975	20010205 <
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PRAI US 2000-548315			B2	20000413	<	
CLASS						
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IIS	US 2002058839 ICM ICS			17		
				-24		
		NCL	5640470	00		
os	MARPAT 136:	363872				
GI						

$$R^2$$
 R^3
 R^4
 R^5
 R^5
 R^5
 R^5
 R^6
 R^6
 R^7
 R^7

AB Methods and compns. are disclosed which use thiourea compds. I (R1, R5 = halo, alkyl, alkoxy, etc.; R2, R4 = halo, alkyl, alkoxy, etc.; R3 = F, H), and alkyl esters thereof, for the treatment of pain. Preparation of I [R1 = F; R2 = Cl; R3-R5 = H] which showed EC50 of 16 nM and 457 nM at α 2B and α 2C receptor in RSAT assay, was given. Particularly disclosed are compns. for the treatment of chronic pain, and methods for their use. ST thiourea prepn adrenergic receptor modulator; analgesic allodynia thiourea

prepn IT Pain

Skin, disease

(allodynia; preparation of thiourea compds. for modulating α -adrenergic receptor activity and use in treatment of pain)

Ι

IT Drug delivery systems

(oral; preparation of thiourea compds. for modulating α -adrenergic receptor activity and use in treatment of pain)

IT Analgesics

Drug delivery systems

Human

Structure-activity relationship

(preparation of thiourea compds. for modulating $\alpha\text{-adrenergic}$ receptor activity and use in treatment of pain)

IT Adrenoceptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) ($\alpha 2A$; preparation of thiourea compds. for modulating

 α -adrenergic receptor activity and use in treatment of pain)

IT Adrenoceptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (α 2B; preparation of thiourea compds. for modulating α -adrenergic receptor activity and use in treatment of pain)

IT Adrenoceptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (α2C; preparation of thiourea compds. for modulating

 α -adrenergic receptor activity and use in treatment of pain)

IT 61290-46-8P 61290-47-9P 61290-44-6P 61290-32-2P 366786-79**-**0P 366786-80-3P 74787-66-9P 366786-78-9P 74548-54-2P 366786-82-5P 366786-83-6P 366786-84-7P 366786-85-8P 366786-81-4P 366786-86-9P 366786-87-0P 366786-89-2P 366786-90-5P

366786-94-9P 366786-91-6P 366786-92-7P 366786-93-8P 366786-98-3P 366786-95-0P 366786-96-1P 366786-97-2P 366786-99-4P 366787-02-2P 366787-03-3P 366787-00-0P 366787-01-1P 366787-04-4P 366787-05-5P 366787-06-6P 366787-07-7P 366787-09-9P 366787-10-2P 366787-12-4P 366787-13-5P 366787-14-6P 366787-15-7P 366787-11-3P 366787-17-9P 366787-18-0P 366787-19-1P 366787-20-4P 366787-16-8P 366787-21-5P 366787-22-6P 366787-23-7P 366787-24-8P 366787-25-9P 366787-28-2P 366787-29-3P 366787-30-6P 366787-31-7P 366787-27-1P 366787-33-9P 366787-34-0P 366787-35-1P 366787-36-2P 366787-32-8P 366787-39-5P 366787-40-8P 366787-37-3P 366787-38-4P 366787-41-9P 366787-45-3P 366787-46-4P 366787-42**-**0P 366787-43-1P 366787-47-5P 366787-48-6P 366787-49-7P 366787-50-0P 366787-51-1P 366787-52-2P 366787-55-5P 366787-53-3P 366787-54-4P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of thiourea compds. for modulating $\alpha\text{-adrenergic}$ receptor activity and use in treatment of pain)

IT 366787-56-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction; preparation of thiourea compds. for modulating α -adrenergic receptor activity and use in treatment of pain)

IT 61290-32-2P 366786-91-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of thiourea compds. for modulating α -adrenergic receptor activity and use in treatment of pain)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
 $CH_2-NH-C-NH-CH_2-CH_2-OH$

- L19 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
- AN 2001:780662 HCAPLUS
- DN 135:327361
- ED Entered STN: 26 Oct 2001
- TI Methods and compositions using benzylthiourea derivatives for modulating alpha adrenergic receptor activity
- IN Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken; Garst, Michael E.; Wheeler, Larry A.

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PA
    Allergan Sales, Inc., USA
SO
    PCT Int. Appl., 28 pp.
    CODEN: PIXXD2
DT
    Patent
    English
LA
IC
     ICM A61K031-00
CC
     1-11 (Pharmacology)
     Section cross-reference(s): 25
FAN.CNT 1
    PATENT NO.
                        KIND
                               DATE
                                          APPLICATION NO.
                                                                 DATE
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                                           WO 2001-US11843
PΙ
    WO 2001078703
                         A2
                               20011025
                                                                  20010411 <--
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                         A3
                               20020321
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            SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
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        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
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    CA 2406057
                               20011025
                                          CA 2001-2406057
                         AA
                                                                  20010411 <--
                               20030205
                                          EP 2001-926876
    EP 1280525
                         A2
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            AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
    JP 2003530430
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                                                                  20010411 <--
    NZ 522027
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PRAI US 2000-548410
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                         Α
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                         W
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CLASS
PATENT NO.
                CLASS PATENT FAMILY CLASSIFICATION CODES
WO 2001078703
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                       A61K031-00
os
    MARPAT 135:327361
GΙ
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$$\mathbb{R}^{1} \xrightarrow{\mathbb{R}^{2}} \mathbb{R}^{3} \xrightarrow{\mathbb{R}^{3}} \mathbb{R}^{0H}$$

AB The invention discloses benzylthiourea derivs. I (R1, R3 = F, H; R2 = C1, H; with provisos, and alkyl esters thereof) as α 2-adrenergic

Ι

II

receptor modulators. The invention also describes the synthesis of a compound II (wherein R1= H, R2= Cl and R3 = F). The effects of these disclosed compds. on acute and chronic pain, their sedative action and their cardiovascular effects are described.

ST alpha adrenergic receptor modulator benzylthiourea deriv prepn analgesic; sedation analgesic benzylthiourea deriv adrenoceptor modulator

IT Pain

Skin, disease

(allodynia; benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT Analgesics

Drug delivery systems

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT Pain

(chronic; benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT Drug delivery systems

(oral; benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT Adrenoceptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

 $(\alpha$ -; benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT 61290-32-2P 61290-44-6P 366786-91-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT 61290-32-2D, alkyl esters 366786-91-6D, alkyl esters

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT 141-43-5, Ethanolamine, reactions 446-48-0, 2-Fluoro benzyl bromide 2740-88-7, 4-Fluoro benzyl isothiocyanate 366787-56-6 RL: RCT (Reactant); RACT (Reactant or reagent)

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

IT 61290-32-2P 366786-91-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$_{\rm CH_2-NH-C-NH-CH_2-CH_2-OH}^{\rm S}$$

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)

(CA INDEX NAME)

C1
$$\begin{array}{c|c} & & & S \\ & & || & \\ & \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \end{array}$$

IT 61290-32-2D, alkyl esters 366786-91-6D, alkyl esters

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

$$C1$$
 \downarrow $CH_2-NH-C-NH-CH_2-CH_2-OH$

L19 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:780661 HCAPLUS

DN 135:298811

ED Entered STN: 26 Oct 2001

TI Thiourea compounds for modulating α -adrenergic receptor activity, preparation, compositions, and use in the treatment of pain

IN Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken;

Garst, Michael E.; Wheeler, Larry A.

PA Allergan Sales, Inc., USA

SO PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

CC 1-11 (Pharmacology)

Section cross-reference(s): 25, 63

FAN.CNT 2

PATENT NO. KIND DATE APPLICATION NO. DATE

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     WO 2001078702
                          A3
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             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
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             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
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     WO 2001-US11842
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CLASS
 PATENT NO.
                CLASS PATENT FAMILY CLASSIFICATION CODES
 WO 2001078702
                 ICM
                        A61K031-00
os
    MARPAT 135:298811
GΙ
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$$R^2$$
 R^3
 R^4
 R^5
 R^5
 R^5
 R^5
 R^5
 R^5
 R^5

(Biological study); PROC (Process)

IT

Adrenoceptors

AB Methods and compns. are disclosed which use thiourea compds. I (R1, R2, R4, R5 = H, OH, C1-3 alkyl, etc.; R3 = H, F), and alkyl esters thereof, for the treatment of pain. Particularly disclosed are compns. for the treatment of chronic pain, and methods for their use. ST thiourea deriv prepn adrenergic receptor modulator; chronic pain treatment thiourea deriv IT Pain Skin, disease (allodynia; thiourea compds. for modulating α -adrenergic receptor activity, preparation, compns., and use in treatment of pain) Drug delivery systems IT (oral; thiourea compds. for modulating α -adrenergic receptor activity, preparation, compns., and use in treatment of pain) IT Analgesics Drug delivery systems Structure-activity relationship (thiourea compds. for modulating α -adrenergic receptor activity, preparation, compns., and use in treatment of pain) IT Adrenoceptors RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(α 2A; thiourea compds. for modulating α -adrenergic receptor activity, preparation, compns., and use in treatment of pain)

Ι

```
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (\alpha 2B; thiourea compds. for modulating \alpha-adrenergic receptor
        activity, preparation, compns., and use in treatment of pain)
IT
     Adrenoceptors
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (\alpha2C; thiourea compds. for modulating \alpha-adrenergic receptor
        activity, preparation, compns., and use in treatment of pain)
IT
     141-43-5, Ethanolamine, reactions
                                         366787-56-6
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (reaction; thiourea compds. for modulating \alpha-adrenergic receptor
        activity, preparation, compns., and use in treatment of pain)
IT
     61290-44-6
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); BIOL (Biological study)
        (thiourea compds. for modulating \alpha-adrenergic receptor activity,
        preparation, compns., and use in treatment of pain)
                  61290-46-8
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     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
     (Uses)
        (thiourea compds. for modulating \alpha-adrenergic receptor activity,
        preparation, compns., and use in treatment of pain)
IT
     61290-32-2 366786-91-6
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
     (Uses)
        (thiourea compds. for modulating \alpha-adrenergic receptor activity,
        preparation, compns., and use in treatment of pain)
RN
     61290-32-2 HCAPLUS
     Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX
CN
     NAME)
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$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-91-6 HCAPLUS
CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

$$C1$$
 \downarrow $CH_2-NH-C-NH-CH_2-CH_2-OH$

L19 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1980:542669 HCAPLUS

DN 93:142669

ED Entered STN: 12 May 1984

TI Synthesis of new biologically active thiourea derivatives

Ι

AU Reiter, J.; Toldy, L.; Schafer, I.; Szondy, E.; Szekely, J.; Dunai-Kovacs, Z.; Borsy, J.; Lukovics, I.

CS Vyzk. Ustav Farm. Chem., Budapest, Hung.

SO Rozvoj Farm. Ramci Ved.-Tech. Revoluce, Sb. Prednasek Sjezdu Cesk. Farm. Spol., 7th (1979), Meeting Date 1977, 121-30 Publisher: Univ.

Karlova, Prague, Czech. CODEN: 430FAO

DT Conference

LA Czech

CC 1-3 (Pharmacodynamics)

GI

AB Twenty-four thioureas [I; R1 = H, F, CF3, or Me; R2 = H or C1-3 alkyl; R3 = H, Me, Et, (CH2)3Me, or (CH2)2OH; n = 2-4] were prepared and screened for diuretic activity in rats. Many I had greater saluretic activity than hydrochlorothiazide and produced a higher Na+-to-K+ ratio in the urine than did the latter. The most active compound was I (R1 = 2-F; R2 = Me; R3 = H; n = 2) [61290-50-4]. Structure-diuretic activity relations are discussed. Most I had hypotensive activity in cats. A related compound, 1-(4-chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)thiourea [61290-76-4], also was one of the most active in this respect.

ST phenylalkylthiourea prepn diuretic antihypertensive; structure activity phenylalkylthiourea diuretic; thiourea deriv diuretic antihypertensive

IT Antihypertensives

Diuretics

(thiourea derivs.)

IT Molecular structure-biological activity relationship (diuretic, of thiourea derivs.)

IT 61290-76-4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antihypertensive activity of)

IT 6098-41-5 29146-63-2 **61290-32-2** 61290-42-4 61290-44-6 61290-46-8 61290-47-9 61290-48-0 61290-50-4 74548-41-7 74548-42-8 74548-43-9 74548-44-0 74548-45-1 74548-46-2 74548-47-3 74548-48-4 74548-49-5 74548-50-8 74548-51-9 74548-52-0 74548-53-1 74548-54-2 74548-55-3 RL: BIOL (Biological study)

(antihypertensive and diuretic activity of)

IT 61290-32-2

RL: BIOL (Biological study)

(antihypertensive and diuretic activity of)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

L19 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1980:532428 HCAPLUS

DN 93:132428

ED Entered STN: 12 May 1984

TI Synthesis of new "benzyl"-thiourea derivatives and their cyclic analogs with diuretic and saluretic activity

AU Reiter, J.; Toldy, L.; Schaefer, I.; Szondy, E.; Borsy, J.; Lukovits, I.

CS Inst. Drug Res., Budapest, Hung.

SO European Journal of Medicinal Chemistry (1980), 15(1), 41-53 CODEN: EJMCA5; ISSN: 0009-4374

DT Journal

LA English

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 6, 25

OS CASREACT 93:132428

GΙ

$$RR^{1}CHN = \begin{pmatrix} R^{2} \\ N \\ X \end{pmatrix}$$

AB RR1CHNHCSNR2R3 [I; R = optionally substituted Ph; R1 = H, Me, Et, Pr, CHMe2, (CH2)6Me, cyclopropyl; R2 = H, Me, Et, Bu, cyclohexyl, CH2CH2OH; R3 = (CH2)3OH, CH2CHMeOH, CH2CMe2OH, CHEtCH2OH, allyl, CH2CMe:CH2, CH2CH2OH] and their cyclic derivs. II (X = CH2, CH2CH2, CH2CHMe, CH2CMe2, CHEtCH2, CH2CH:CH) with diuretic and saluretic activity were prepared Thus, RR1CHNH2 were converted to RR1CHNCS or RR1CHNHCS2Me, which were treated with R2R3NH to give I. Acidic cyclizaton of I using HCl gave II. The quant. structure activity relationships for I and II were determined using the Free-Wilson approach.

ST benzylthiourea diuretic saluretic prepn; benzylthiazolidine diuretic prepn; thiazolidine benzyl diuretic prepn; benzylamine isothiocyanation; isothiocyanates alkylamine reaction; carbaminodithioate alkylamine reaction; thiourea benzyl prepn cyclization

IT Diuretics

(benzylthioureas and benzylaminothiazolidines)

IT Molecular structure-biological activity relationship

(diuretic, of benzylthioureas and benzylaminothiazolidines)

IT 13578-57-9P 13677-15-1P 13846-58-7P 30480-73-0P 61290-51-5P

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   (preparation and diuretic and saluretic activity of)
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74788-81-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
   (preparation of)
             13677-11-7P 61290-32-2P
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74787-96-5P
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(Reactant or reagent)
   (preparation, cyclization, and diuretic activity of)
61290-44-6P
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(Reactant or reagent)
   (preparation, cyclization, and diuretic and saluretic activity of)
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                                                 16735-69-6
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22623-45-6
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74788-78-6
RL: RCT (Reactant); RACT (Reactant or reagent)
   (reaction of, with amines)
                                109-83-1
                                           110-73-6
                                                       111-42-2, reactions
78-96-6
          96-20-8
                    107-11-9
111-75-1
           141-43-5, reactions
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2878-14-0
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   (reaction of, with isothiocyanate or carbaminodithioates)
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                               100-46-9, reactions
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74788-46-8
RL: RCT (Reactant); RACT (Reactant or reagent)
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IT

IT

IT

IT

IT

IT

(reaction of, with isothiocyanates or carbonodithioates)

IT 61290-32-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation, cyclization, and diuretic activity of)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

L19 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1977:16440 HCAPLUS

DN 86:16440

ED Entered STN: 12 May 1984

TI Benzylthiourea diuretics

IN Reiter, Jozsef; Toldy, Lajos; Borsi, Jozsef; Schaefer, Inge; Szondy, Eleonora; Szekely, Jozsef

PA E. Gy. T. Gyogyszervegyeszeti Gyar, Hung.

. SO Ger. Offen., 49 pp.

CODEN: GWXXBX

DT Patent

LA German

IC C07C157-02

CC 25-21 (Noncondensed Aromatic Compounds)

FAN.CNT 1

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	BE	839502	A1	19760701	BE	1976-165107	19760312 <		
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	FR	2303532	B1	19781215					
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PRAI	HU	1975-GO1303	A	19750314	<				
CLASS	3								

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

DE 2610865 IC C07C157-02

AB RR1C6H3CHR2NHCSNR3R4 [I; R, R1 = H, OMe, CF3, Cl, etc.; R2 = C1-7 alkyl; R3 = H, alkyl, CH2CH2OH; R4 = allyl, CH2CH2OH, (CH2)3OH)] were prepared by reacting R3R4NH with RR1C6H3CHR2X (X = NCS, NHCSCl).. Thus, 4-FC6H4CH2NCS in CHCl3 was added to HOCH2CH2NH2 in CHCl3 at 0°, and the mixture was refluxed for 1 hr to give 100% 4-FC6H4CH2NHCSNHCH2CH2OH. About 65 other I were prepared, useful as diuretics, as shown by tests on rats.

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ST
     diuretic benzylthiourea; thiourea benzyl diuretic
IT
    Diuretics
        ((hydroxyalkyl)benzylthioureas)
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                             61290-40-2P 61290-42-4P
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     61290-44-6P
                  61290-45-7P
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                                               61290-53-7P
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     74787-95-4P
     RL: SPN (Synthetic preparation); PREP (Preparation)
        (preparation of)
IT
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     RL: SPN (Synthetic preparation); PREP (Preparation)
        (preparation of, and reaction with amines)
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                          61290-95-7 61290-96-8
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TT
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        (reaction of, with fluorobenzylamine)
TТ
     109-83-1
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (reaction of, with isothiocyanates)
TТ
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        (reaction of, with thiophosgene)
     141-43-5, reactions
IT
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IT
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        (preparation of)
RN
     61290-32-2 HCAPLUS
     Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX
CN
     NAME)
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